

## REMARKS

### I. Introduction

Claims 36-38 and 41-55 are pending in this application. Claims 1-35, 39-40, and 56-94 have been previously canceled. Claim 37 has herewith been canceled and incorporated into claim 36. Claims 36, 38, 41, 47, 50, 52, 54, and 55 have been amended to clarify the claims and to correct informalities. Claim 95 has been added to further limit claim 38. No new matter has been added in the amendments. Claim 50 has been amended to further limit the claim and correctly recite the carbon concentration in the medium. Claim 54 has been amended to correctly recite the broth volume. Support for amended claims 36 and 55 can be found at page 1, paragraph 4 and page 2, paragraph 3 of the specification. Support for amended claim 38 can be found at page 3, paragraph 1 of the specification. Support for amended claim 50 can be found at page 3, paragraph 3 of the specification. Support for amended claim 54 can be found at page 4, paragraph 3 of the specification. Support for new claim 95 can be found at page 3, paragraph 1 of the specification.

Applicants thank the Examiner for withdrawing the finality of the previous Office Action pursuant to 37 CFR § 1.114.

### II. Rejections Under 35 U.S.C. § 102(b)

The Examiner has rejected claims 36-38, 42-45, 47, 49, and 51-52 under 35 U.S.C. § 102(b) as being anticipated by Cole *et al.* (U.S. Patent No. 4,110,165). The Examiner has alleged that the processes of Examples 9 and 13 in Cole *et al.* meet the limitations of the claimed invention requiring that a microorganism be grown within the claimed phosphorus concentration range of 0.0015% and 0.15% and requiring a decrease in the phosphorus concentration.

Applicants respectfully traverse this rejection. In order to reject a claim under 35 USC § 102, the examiner must demonstrate that each and every claim limitation is contained in a single prior art reference. *See Scripps Clinic & Research Foundation v. Genentech, Inc.*, 18 USPQ2d 1001, 1010 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 90 (Fed. Cir. 1986). Not only must the claim limitations be present, but an allegedly anticipatory reference must enable the person of ordinary skill in the art to practice the invention as claimed. Otherwise, the invention cannot be said have been already within the public's possession, which is required for anticipation. *See Akzo, N.V. v. U.S.I.T.C.*, 1 USPQ2d 1241, 1245 (Fed. Cir. 1986); *In re Brown*, 141 USPQ 245, 249 (CCPA 1964).

*Cole et al.* teach the cultivation of *Streptomyces clavuligerus* in a fermentation medium comprising assimilable sources of carbon, nitrogen, and mineral salts, wherein soy flour may be used as the nitrogen source. *Cole et al.* disclose a maximum yield of clavulanic acid obtained within 2-10 days, with peak yields of clavulanic acid obtained within 5 days and an optimum titre of clavulanic acid achieved between 3-5 days.

Applicants submit that *Cole et al.* do not specifically teach that the concentrations in Examples 9 (concentration of  $K_2HPO_4$  = .2% w/v) or in Example 13 (concentration of  $KH_2PO_4$  = 0.1% w/v) are present when fermentation begins, as required in the claimed invention. Furthermore, *Cole et al.* do not specifically teach that the fermentation comprises a growth phase and a stationary phase, that the assimilable phosphorus concentration is maintained under 0.15% w/v, or that assimilable phosphorus is allowed to decrease after cessation of the growth phase, as in Applicants' amended claims 36 and 55. Claim 36 has been amended to recite in part (a) a fermentation comprising "a growth phase and a stationary phase" and in part (b) a "growth phase, after which the concentration of said assimilable phosphorus is allowed to decrease". *Cole et al.*

do not teach *maintaining* the phosphorus concentration below 0.15% w/v during the growth phase of the fermentation, as in the claimed invention. Cole *et al.* do not specifically teach that no additional phosphorus is added during fermentation, but rather, that "phosphoric acid may be added to the media ... particularly if chemically defined" (col. 10, lines 55-57). Given the above distinctions, applicants submit that Cole *et al.* do not meet the limitations of the claims, and do not enable the practice of the claimed invention. Accordingly, Cole *et al.* do not place the claimed invention in the possession of the public, and thus the rejection should be withdrawn.

### **III. Rejections Under 35 U.S.C. § 103(a)**

#### **A. Claims 36-38, 41-47, and 49-54 in view of Cole *et al.***

The Examiner has rejected claims 36-38, 41-47, and 49-54 under 35 U.S.C. § 103(a) as being unpatentable in view of Cole *et al.* (U.S. Pat. No. 4,110,165). The Examiner has alleged that it would have been *prima facie* obvious to one of ordinary skill in the art to successfully produce the claimed invention by substituting the missing elements in Cole *et al.* with those of the claimed invention, through routine experimentation. Such missing elements include a phosphorus concentration of about 0.008% recited in claim 41, the range of carbon source concentrations recited in claim 50, the use of Na<sub>2</sub>PO<sub>4</sub> instead of KH<sub>2</sub>PO<sub>4</sub> as an assimilable phosphorus source, as recited in claim 46, or large volume fermentations as recited in claims 53 and 54.

Applicants respectfully traverse the Examiner's § 103 rejections. Applicants again remind the Examiner that M.P.E.P. § 2142 sets forth three requirements that must be met in order to establish a *prima facie* case of obviousness under § 103. First, there must be some suggestion or motivation, either in the references themselves, or in the knowledge generally available to one

of ordinary skill in the art, to modify or combine the references. Second, there must be a reasonable expectation of success upon combining such references. Finally, the prior art references, when combined, must teach or suggest all of the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on the Applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988); *W.L. Gore v. Garlock, Inc.*, 220 USPQ 303, 312-13 (Fed. Cir. 1983) (it is improper in combining references to hold against the inventor what is taught in the inventor's application); *see also* M.P.E.P. §§ 2142-43 (February 2003). Thus, the Examiner must provide evidentiary support based upon the contents of the prior art to support all facets of the rejection, rather than just setting forth conclusory statements, subjective beliefs, or unknown authority. *See In re Lee*, 277 F.3d 1338, 1343-44 (Fed. Cir. 2002).

When an Examiner alleges a *prima facie* case of obviousness, such an allegation can be overcome by showing that (i) there are elements not contained in the references or within the general skill in the art, (ii) the combination is improper (for example, there is a teaching away or no reasonable expectation of success) and/or (iii) objective indicia of patentability exist (for example, unexpected results). *See U.S. v. Adams*, 383 U.S. 39, 51-52 (1966); *Gillette Co. v. S.C. Johnson & Son, Inc.*, 16 USPQ2d 1923, 1927 (Fed. Cir. 1990); *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve*, 230 USPQ 416, 419-20 (Fed. Cir. 1986). Applicants submit that the rejections do not meet this test.

Applicants submit that one of ordinary skill in the art would not have been motivated to successfully produce the claimed invention through routine experimentation and thereby arrive at "suitable" concentrations of 0.008% phosphate, as in claim 41, based on the teachings of Cole *et*

*al.* The initial burden is on the Examiner to provide some suggestion of desirability ...". "To support the conclusion that the claimed invention is directed to obvious subject matter, either the reference must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985).

While Cole *et al.* teach the use of several types of phosphorus salts in the fermentation medium such as  $K_2HPO_4$  and  $KH_2PO_4$ , Cole *et al.* do not teach the desirability or even the *necessity* of using phosphorus in a fermentation medium. Cole *et al.* merely teach that " $Na^+$  or  $K^+$  salts of phosphoric acid *may* be added" (emphasis added) (col. 10, lines 55-57). Even if Cole *et al.* did specifically teach the desirability of using phosphorus in the claimed invention, the mere desirability of using phosphorus in the fermentation media is not sufficient motivation to prompt one of ordinary skill in the art to add phosphorus at a concentration of 0.0015% w/v to less than 0.15% w/v to the fermentation medium, as in the claimed invention. Applicants' invention can therefore be distinguished on the basis that phosphorus in the fermentation medium contributes to the successful beginning, maintenance, and completion of the claimed clavulanic acid fermentation.

The claimed invention yields the unexpected result of an above-average clavulanic acid yield when the concentration of assimilable phosphorus is maintained below 0.15% w/v, compared to Cole *et al.* For example, in the claimed invention, 3580 mg/l of clavulanic acid was produced (p. 10, paragraph 2 of the specification), compared to maximum yields of 200-300  $\mu$ g/ml of clavulanic acid taught by Cole *et al.* in Example 12 (col. 23, lines 48-52) and 300-500  $\mu$ g/ml clavulanic acid in Example 13 (col. 24, lines 3-4). This unexpected result of the claimed

invention was not the result of routine experimentation. Nor did this unexpected result arise either from the starting phosphorus concentration or from the substitution of one clavulanic acid-producing species for another. Rather, this unexpected result was caused by the addition of phosphorus during the growth phase of the fermentation and the maintenance of the phosphorus concentration below 0.15% w/v (page 2, paragraph 3 of the specification), after which the phosphorus concentration was allowed to decrease, preferably to 0.00 % w/v by about 40 hours of fermentation.

Applicants have rendered moot the Examiner's rejections of the claimed carbon concentration as a result of Applicants' amendment to claim 50. Applicants' claimed carbon concentration is outside of the range that the Examiner noted at Col. 10, lines 39-42 because it does not include 5% w/v.

One of ordinary skill in the art would not have been motivated to substitute the assimilable phosphorus source of  $\text{NaH}_2\text{PO}_4$  in claim 46 of the claimed invention for the  $\text{K}_2\text{HPO}_4$  or  $\text{KH}_2\text{PO}_4$  assimilable phosphorus source taught in Cole *et al.* Even though Cole *et al.* teach at col. 10, lines 55-57 that either of the salts of phosphoric acid may be added to the medium, this does not necessarily mean that one of ordinary skill in the art would be motivated to substitute  $\text{Na}^+$  for  $\text{K}^+$  or would reasonably expect the salts of potassium and sodium to "function substantially equivalently" in the processes disclosed by Cole *et al.* because  $\text{NaH}_2\text{PO}_4$ ,  $\text{KH}_2\text{PO}_4$ , and  $\text{K}_2\text{HPO}_4$  have different properties in water.  $\text{NaH}_2\text{PO}_4$ , the preferred phosphorus source used in the claimed invention is "freely soluble in water", while the solubility of  $\text{K}_2\text{HPO}_4$  in Example 9 is only "very soluble", and  $\text{KH}_2\text{PO}_4$  used in Example 13 of Cole *et al.* is even worse at "4.5 parts water" (The Merck Index, 13, 2001, p. 1371, nos. 7743, 7744, and 8734).

One of ordinary skill in the art would not have been motivated to successfully use large

volume fermentations, as recited in claims 53 and 54, in the processes disclosed by Cole *et al.*, even if allegedly economically advantageous, because Cole *et al.* teach that this would be disadvantageous to do so. Cole *et al.* teach that when fermentation of clavulanic acid was attempted on a larger scale, fermentation "was slower and optimum  $\beta$ -lactamase inhibitory activity was achieved 7-9 days after inoculation" (col. 19, lines 21-25) as opposed to the more optimal time of 3-5 days taught in Cole *et al.* (col. 9, lines 56-57; col. 20, lines 18-20; col. 21, lines 49-50; col. 20, lines 38-40). Cole *et al.* cultivated *Streptomyces clavuligerus* in 2 liter flasks containing the same medium and cultural conditions used in 500 ml flasks. However,  $\beta$ -lactamase inhibiting activity of *Streptomyces clavuligerus* in the 2 L flasks was significantly reduced compared with the 500 ml flasks. For example, in the 2,000 ml flask, the  $\beta$ -lactamase inhibition rates were 10-36% compared to 50-57% in the 500 ml flask. This shows that larger batch fermentations are not desirable because they result in decreased  $\beta$ -lactamase inhibition, thereby producing decreased yields of clavulanic acid, compared to smaller batch fermentations. Thus, it would not be likely that one of ordinary skill in the art would be motivated to conduct a large scale fermentation of clavulanic acid, as in the claimed invention, because the fermentation process would take more time and the clavulanic acid yields would be much lower, both of which would cause increased costs.

Applicants respectfully submit that Cole *et al.* do not expressly or impliedly suggest any of claims 36-38, 41-47, and 49-54 of the claimed invention for the above mentioned reasons, and the Examiner's line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references is not convincing. Applicants therefore respectfully request that this rejection be withdrawn.

**B. Claims 36-38 and 41-55 in view of Cole *et al.* and Stanbury *et al.***

The Examiner has further rejected claims 36-38 and 41-55 under 35 U.S.C. § 103(a) as being unpatentable over Cole *et al.* (U.S. Pat. No. 4,110,165) in view of Stanbury *et al.* The Examiner has asserted that while Cole *et al.* do not disclose conducting fed-batch or continuous process fermentations as recited in claims 48 and 55, one of ordinary skill in the art would have been motivated to use a 0.1% w/v phosphorus concentration in a fed-batch or continuous process production of clavulanic acid because Cole *et al.* disclose that this concentration is desirable in fed-batch fermentations which produce antibiotics such as penicillin disclosed by Stanbury *et al.*, and clavulanic acid is similar to penicillin.

Applicants respectfully traverse this rejection and point out that as mentioned previously, it would not be obvious to one of ordinary skill in the art to produce clavulanic acid in large volume fermentations in view of Cole *et al.* because Cole *et al.* teach that when fermentation of clavulanic acid was attempted on a larger scale, fermentation "was slower and optimum  $\beta$ -lactamase inhibitory activity was achieved 7-9 days after inoculation" (col. 19, lines 21-25). Furthermore, clavulanic acid is not so functionally identical or even similar to penicillin that one of ordinary skill in the art would be motivated to substitute it for the penicillin in the fed batch process allegedly taught by Stanbury *et al.* Clavulanic acid has essentially no antibacterial activity by itself<sup>1</sup> and usually has to be paired up with a beta lactam such as amoxicillin to be effective, whereas penicillin is usually always used alone because it is much more effective. Accordingly, the skilled person would not extrapolate penicillin processes to clavulanic acid.

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<sup>1</sup> <http://www.vet.purdue.edu/depts/bms/courses/mcmp611/chmr/penems.htm>; *Proc Natl Acad Sci USA*, 1998 Aug 4;95(16):9082-6.



Therefore, because it would not be obvious to combine Cole *et al.* with Stanbury *et al.* to produce the claimed invention for the above-mentioned reasons, Applicants request that this rejection be withdrawn.

**C. Claims 36-38 and 41-55 in view of Cole *et al.*, Stanbury *et al.*, and Puentes *et al.***

The Examiner has rejected claims 36-38 and 41-55 under 35 U.S.C. § 103(a) as being unpatentable over Cole *et al.* (U.S. Pat. No. 4,110,165) in view of Stanbury *et al.*, and further in view of Puentes *et al.* The Examiner has stated that although neither Cole *et al.* or Stanbury *et al.* disclose clavulanic acid production from all of the microorganisms recited in claim 47, one of ordinary skill in the art would have reasonably expected that the microorganisms disclosed in Puentes *et al.* could produce clavulanic acid in the fermentation media disclosed by Cole *et al.*

Applicants respectfully traverse this rejection and point out that the claimed invention is unobvious under 35 USC § 103(a) because, among other things, the starting concentration of phosphorus and the addition of phosphorus during the growth phase of fermentation, followed by the further limitations in the dependent claims of the claimed invention are not disclosed or suggested by Cole *et al.*, as mentioned previously, either alone or in combination with, or in view of Puentes *et al.*

Cole *et al.* disclose various concentrations of assimilable phosphorus: 0.2% w/v  $K_2HPO_4$  in Example 9, 0.1% w/v  $KH_2PO_4$  in Example 12 (yielding 200-300  $\mu\text{g/ml}$  of clavulanic acid), and 0.1%  $KH_2PO_4$  w/v in Example 13 (yielding 300-500  $\mu\text{g/ml}$  of clavulanic acid). While Cole *et al.* teach that phosphate *should* be included in the fermentation medium, the Examples in Cole *et al.* do not teach that phosphorus addition is essential or that phosphorus *was* added during the fermentation phase, or subsequently during the growth phase. Nor do Cole *et al.* show any

relationship between the phosphate present in the starting medium or the addition of phosphate and the yield of clavulanic acid achieved.

Puentes *et al.* allegedly teach control of catabolite repression through the production of impure clavulanic acid in relatively low yields using available fermentation and purification techniques. While Puentes *et al.* teach all of the *Streptomyces* species of claim 47, the source of assimilable carbon in the fermentation medium of Puentes *et al.* is kept at 0-2% upon fermentation, and upon addition of assimilable carbon during the fermentation process, the concentration is kept below 1%. In contrast, the assimilable carbon of Applicants' claimed invention is greater than 5% w/v, per amended claim 50. Example 1 of Puentes *et al.* discloses a starting concentration of  $\text{KH}_2\text{PO}_4$  of 0.1%, yielding 1,403  $\mu\text{g/ml}$  of clavulanic acid. Examples 2 and 3 and the Comparative Examples in Puentes *et al.* show the effect of the addition of assimilable carbon (glycerol) during the fermentation. Example 4 shows a clavulanic acid yield of 1,424  $\mu\text{g/ml}$ . However, Puentes *et al.* do not teach fermentation broth volumes as large as the claimed invention. Nor do they teach any relationship between the starting phosphorus concentration and the clavulanic acid yield or the addition of phosphorus during fermentation, both of which are crucial and essential to the success of the claimed invention.

In contrast, the claimed invention clearly discloses that the growth of a clavulanic acid-producing organism may include two phases: a growth phase and a stationary phase. The growth phase may be completed in less than 2 days (about 40 hours) in a typical clavulanic acid fermentation of 5-6 days. During the growth phase, biomass is produced, and the phosphorus concentration of the claimed invention is preferably maintained below 0.15% w/v, after which it may be allowed to decrease. During the stationary phase growth does not occur, and metabolites such as clavulanic acid are predominantly produced.

Furthermore, the starting fermentation medium of the claimed invention contains phosphorus in a lower concentration than the prior art. In Example 1B, 5 kg (0.0083%) of  $\text{NaH}_2\text{PO}_4$  is added to the starting medium, and phosphate is added during the growth phase to maintain the phosphorus concentration below 0.15% w/v which brings about improved yields of clavulanic acid not taught in the prior art. Example 1 of the claimed invention discloses a 96 hour fermentation period, yielding 3,580  $\mu\text{g/ml}$  of clavulanic acid.

Applicants submit that the above identified combinations of references are nowhere supported by the references or in the common knowledge of the art. In *In re Rouffet*, 149 F.3d 1350 (Fed. Cir. 1998), the Federal Circuit stated that “virtually all [inventions] are combinations of old elements.” *Environmental Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 698, 218 USPQ 865, 870 (Fed. Cir. 1983); *see also Richdel, Inc. v. Sunspool Corp.*, 714 F.2d 1573, 1579-80, 219 USPQ 8, 12 (Fed. Cir. 1983) (“Most, if not all, inventions are combinations . . . mostly of old elements”). Therefore an Examiner may often find every element of a claimed invention in the prior art just as we could likely find every word in a dictionary. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an Examiner to use the claimed invention itself as a blueprint to defeat the patentability of the claimed invention. Such an approach would be an “illogical and inappropriate process by which to determine patentability.” *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570, 38 USPQ2d 1551, 1554 (Fed. Cir. 1996).

To prevent the use of hindsight based on the invention to defeat patentability of the invention, the Federal Circuit requires the Examiner to show motivation to combine the references that create the case of obviousness. In other words, the Examiner must show reasons

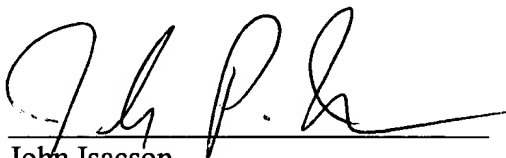
that the skilled artisan, confronted with the same problems as the inventors and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed. *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998).

Applicants submit that the above-mentioned rejections do not satisfy the strictures of the *Rouffet* decision. The primary references are not combinable without proscribed hindsight. The secondary references do not rectify the deficient and contradictory teachings of the primary references, and therefore Applicants respectfully request that the obviousness rejections described above be withdrawn.

#### **IV. Conclusion**

In view of the foregoing remarks and amendments, reconsideration of this application and allowance of the claims are respectfully requested. If any issues remain which the Examiner believes could be resolved through a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at 202-912-2777.

Respectfully submitted,



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May 19, 2004  
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